Remarks/Arguments

1. Applicant thanks Examiner for the careful review of the present application, as evidenced by the Office Action of March 27, 2008. In that Office Action, Examiner rejected all pending claims 5 –11.

2. **Co-Pending Application: U.S. Patent Application No. 10, 570,920**, filing date May 19, 2006, is co-pending with this application. A set of currently pending claims is attached to this paper.

3. **Amendments to the Specification:** A sentence in paragraph [0007] was amended to read "in a suspended state, completely surrounded by the fluid." Support for the insertion of the words "completely surrounded" is found in the original claim 1 of PCT patent application, which claimed "the organ (2) covered by an impermeable protective cover (21) and furthermore completely surrounded by a storage fluid (4)." This language is part of the initial disclosure and its inclusion here in the Specification introduces no new subject matter. The word "floating" in the same paragraph was replaced with the word "suspended" and the word "completely" moved to modify surrounded. These changes are merely a correction of the translation from the German. The word "schwebend" is typically translated as suspended or floating. In this case, "suspended" is the more accurate translation. The word "supply" in Paragraph [0008] was amended to read "maintain." This also is merely a correction of the translation of the original text. The original German word "versorgen" has several meanings, one of which is "supply" and another of which is to "maintain" or "support." In this context, the more accurate translation for "versorgen" is the word "maintain." These

amendments introduce no new subject matter and Applicants respectfully request approval and entry of the amended paragraphs.

4. **Amendments to the Claims:** The second paragraph in the body of claim 1 was amended primarily for purposes of simplification, whereby the subject matter remains the same. The final paragraph in the body of the claim was amended to clarify that the organ is maintained in a "suspended state inside said protective cover and, except for the portion of the chamber wall with the connectors, completely surrounded by said storage fluid." Support for this amendment is found in the original claim 1 of the PCT patent application and also in FIG. 1, which shows the cover attached to the wall that has the connectors to the blood vessels. See the Literal Translation of the PCT Application PCT/DE2004/001944, Claim 1. Claim 11 was amended to correspond with a previous amendment of claim 1, in which the word "sack" was replaced with "cover." These amendments introduce no new subject matter and Applicant requests approval and entry of the amended claims.

5. **Clarification of Inventive Features: Prior art:** Applicants provide a brief description of the well known technology of maintaining vitality of an extracorporeal liver that is intended for a transplant and then a brief review of the relevant inventive features of the invention as claimed in the currently pending claims and as described in the Specification and FIG. 1. Applicants note that the person of ordinary skill in the art is one who is familiar with preparing and maintaining organs for transplant surgery. Attached to this paper are:

Attachment A: A user data sheet for a bicarbonate hemofiltration solution, manufactured by B. Braun of Glandorf, Germany, plus an English-language translation of the sheet. This Attachment is provided, to show that the dialysate used in the

process of maintaining the vitality of an extracorporeal organ destined for transplant is a watery salt solution.

Attachment B: Two data sheets showing the density of water at various temperatures. One sheet is in German, but is provided because it shows the density of water at 37°C. The second sheet is the Engineering Data Software, downloaded from the Internet site at www.engineeringtoolbox. com, and is provided as an additional English-language reference on the well known densities of water at various temperatures.

Attachment C: Article written by Bodo Klarmann, "Über die Ermittlung der Dichte wäßriger Salzlösungen" ["On the Determination of the Density of Watery Salt Solutions"], published in the *Fresenius' Journal of Analytical Chemistry*, Berlin / Heidelberg, Vol. 130, Nos. 2 – 3, January 1950, pp. 186 – 192. This article shows that it was known at least as far back as 1950 to adjust the density value of a watery salt solution by adjusting the amount of salt added. An English-language translation is provided.

Attachment D: Article written by W. A. Nadeshdin, „Zur Untersuchung der Minderwertigkeit der Organe an Leichen" ["On the Study of the Inferiority of Organs on Corpses"], published in the *International Journal of Legal Medicine*, Berlin / Heidelberg, Vol. 18, No. 1, December 1932, pp. 426 – 431. Excerpts from this article relating to the density or specific weight of the liver are provided in an English-language translation. This article shows that persons of skill in the art have known since 1932 that the density of the healthy liver is 1.065.

6. The dissertation by Michael R. Schön (also written as Schoen) mentioned in the Specification and listed in a previously filed IDS is the closest prior art. Schön teaches placing the organ in an organ perfusion chamber that is filled with water that is heated to

a certain temperature. Heated water is circulated through the chamber to maintain the desired temperature. See "Transplantation von Lebern nicht-herzschlagender Spender im Schweineleber-Transplantationsmodell," Habilitationsschrift [published dissertation] 1999, Humboldt Universitaet zu Berlin, pages 16 – 18 and 39 – 40. A translation of two paragraphs from pages 39 and 40 is attached to this paper. A translation of the other cited pages was previously submitted with the IDS filed on December 20, 2007.

7. This Schön prior art is widely known in the field of organ transplant surgery. A subsequent article describing this method of perfusion using a water-filled perfusion chamber was published in the English language in 2001 by Lippincott Williams & Wilkins, Inc. in the Annals of Surgery, an internationally renowned surgery journal. See: "Liver Transplantation after Organ Preservation with Normothermic Extracorporeal Perfusion," by Michael R. Schön et al., The Annals of Surgery Vol. 233, No. 1, pages 114 – 123. See specifically page 115, second column, bottom paragraph: "The liver was placed in a sterile plastic bag, which was then immersed in a 37 degree C warm water bath in a specially designed perfusion chamber." This article was submitted to the USPTO in an IDS with a Preliminary Amendment on May 19, 2006.

8. It is known that the liver has three blood vessels, namely, the *Arteria hepatica*, the *Vena poartea*, and the *Vena cava*. These three vessels are hooked up to a perfusate circulation system for the purpose of liver perfusion, such that prepared, cleansed blood is pumped into the *Arteria hepatica* as well as into the *Vena poartea*. Metabolic processes take place in the liver and the blood exits the liver again at the end via the *Vena cava*. The metabolic waste products contained in the exiting blood are removed from the blood with the help of a dialyzer, which is connected to a dialysis circulation system. Because the dialysate can only take up a limited amount of

metabolic waste, it must be continually replenished with fresh dialysate and, thus, it is necessary to hook a large reservoir into the dialysis circulation system, in order to add fresh dialysate as needed. Applicants refer Examiner to the Michael Schön dissertation and the Annals of Surgery article, which illustrate the basic method of perfusing an organ and dialyzing the perfusate.

9. As Examiner correctly recognizes, and as is well known from the prior art, a dialyzer comprises in principle two chambers that are separated from each other by a semi-permeable membrane. During dialysis, blood (or perfusate, which in this case is blood with electrolytes added to it) flows through one of the chambers. This blood (perfusate) contains a high concentration of metabolic waste products or toxins. Dialysate having no or very little metabolic waste products or toxins flows through the other chamber. As the perfusate and dialysate fluids are flowing through the dialyzer, the blood/perfusate releases the metabolic waste products by means of diffusion through the semi-permeable membrane into the dialysate. The dialyzer is not shown in the drawing, because its function is well known and furthermore, the particular method of dialysis is irrelevant to the inventive storage system at issue here.

10. With the Schön system, water is used in the organ perfusion chamber to maintain the desired temperature of the organ. The "sterile liver" is enclosed dry, that is, without any other fluid added to it, in an air- and water-tight protective cover, so that it does not come into direct contact with the water. The protective cover is attached to the wall of the chamber to provide a complete barrier between organ and water. Water has a somewhat lower density than the liver, so the liver will naturally sink in the water. This is prevented, however, by the flexible sack, which is attached to the wall of the chamber. The water provides some buoyancy to the liver, so that the force with which

the wall of the sack presses against the liver is only a portion of the dead weight force of the liver and, thus, the flexible sack is capable of supporting the buoyant weight of the liver.

11. **Inventive Features:** The storage system of the present application claims an organ perfusion chamber that is filled with a storage fluid that is a dialysate and also that the organ is enclosed in a protective cover and maintained in a suspended state in the storage fluid, such that it is essentially completely surrounded by the storage fluid, that is, completely surrounded with the exception of the small area of the wall that has the tubes that connect to the blood vessels of the organ being stored in the chamber. In other words, the inventive elements relative to the closest prior art of the Schön perfusion chamber and system are: 1) storing dialysate fluid in the perfusion chamber, and 2) suspending the organ to be perfused, enclosed in a protective cover, in the dialysate storage fluid. A further inventive element includes integrating heating elements into the walls of the organ perfusion chamber.

12. Of note is that the Schön system of maintaining an organ for subsequent transplant requires three circulating fluid systems: a perfusate circulation system; a dialysate circulation system; and a heated water system. By contrast, the present invention requires only two fluid circulation systems: a perfusate circulation system and a dialysate circulation system, whereby the organ perfusion chamber serves a dual purpose: one, to hold the organ essentially surrounded by a heated fluid, so as to maintain the organ at the desired temperature; and two, to serve as a reservoir for replenishment dialysate that flows into the dialysate circulation system as needed. This is a simplification of previously known systems, a simplification which provides several advantages that are discussed below.

13. **Dialysate:** Dialysate is a watery salt solution, the density of which can be adjusted to be similar to that of the organ being stored (in this case, a liver). Please refer to Attachment A, enclosed with this paper, for information on a commercially available dialysate that is a watery salt solution, Attachment B for data on the density of water; Attachment C for a discussion on determining and adjusting the density of a watery salt solution; and Attachment D for a discussion of the specific weight of the healthy liver. It has long been known that the density of water at 37 degrees C has a density slightly less than 1, that at the same temperature, watery salt solutions have a density greater than 1, and that the density of a healthy liver is approx. 1.065. See Nadeshdin (1932), p. 429, paragraph 4. Further it is known that the density of a watery salt solution can be adjusted by adjusting the amount of salt in the watery solution according to the equation disclosed in Klarmann (1950), p. 186. Thus, the technique of adjusting the density of a watery salt solution was well known to persons of skill in the art. Furthermore, once the person of skill in the art has been instructed to suspend an organ in a watery salt solution, he or she would have known how to adjust the density of that watery salt solution to support the organ above the floor of the container.

14. Because the density of the dialysate can be adjusted to correspond to the density of the liver, the liver is able to be held in a suspended state surrounded by the fluid, protected from the dialysate by the protective cover. In practice, it is unavoidable that slight deviations occur between the density of the liver and that of the dialysate. Is the density of the liver lower than that of the dialysate, then it "swims" or floats; is the density higher, than the liver "sinks". Because of the density of the dialysate, however, these differences are minimal and the protective cover is able to take up the slight weight forces to maintain the organ in a suspended state, that is, from sinking to the floor of the chamber, and without creating damaging pressure points on the liver tissue.

15. **Advantages of Inventive Storage System:** The advantages of the storage system according to the invention include a technical simplification of the system, resulting from the elimination of the water circulation system, which translates to a cost savings. A further advantage results in better temperature regulation of the overall system. By regulating the temperature of the dialysate stored in the reservoir, the temperature of the organ chamber is maintained at the desired temperature. Feeding warmed dialysate into the dialysate circuit also has a positive effect on the temperature control of the dialysate in circulation. A third advantage lies in the buoyancy of the dialysate, which is greater than that of water, and the ability to adjust the density of the dialysate to correspond to the density of the organ being stored. This makes it easier to maintain the organ in a floating or suspended state, and minimizes the weight forces exerted by the protective cover against the organ, should slight differences between the densities of the storage fluid and the organ occur. This minimizes a source of tissue damage, which can possibly result from the pressure exerted on the organ tissue by the protective cover, when the organ is supported in water.

16. Applicants note for clarification that FIG. 1 is a top plane view of the organ in the perfusion chamber, not a side elevational view. Furthermore, the area of the passages for the blood vessel connectors through the chamber wall is shown with some exaggeration, in order to make it easier to recognize the five conduits. The blood vessel connectors that are guided through the chamber wall are conventionally flexible hoses and bear virtually none of the weight forces of the liver, as this would exert unwanted forces in undesirable locations on the liver. This exaggerated illustration should not mislead one to think that the liver or the particular organ being stored in the chamber is firmly supported by the wall that is fitted with the inlets and outlets. In actuality, in the conventional perfusion chamber, this area takes up only a small portion of the

corresponding chamber wall and the connectors are constructed so as to exert no or only extremely slight forces on the organ.

17. **Rejections under 35 U.S.C. § 112:** Examiner rejected claims 5 – 11 as based on a disclosure that is not enabling, because the language "wherein said organ is maintained by the storage fluid in a floating state inside said protective cover" is critical to the invention and is not enabled by the disclosure.

18. The disclosure clearly describes and illustrates the liver enclosed in a protective cover and placed in the perfusion chamber. See FIG. 1 and amended paragraph [0007], which describes the organ as maintained in a suspended state and completely surrounded by the storage fluid. From this description, a person of ordinary skill in the art will know that the perfusion chamber is filled with a fluid. Further, it is generally known that dialysate has a density significantly greater than that of water and slightly less than that of a liver or organ and that the density of the dialysate may easily be adjusted to correspond to the density of the liver or organ. In the ideal case, the density of the dialysate is equal to that of the liver. Thus, the dialysate exerts a buoyancy force on the liver that is sufficient to maintain the organ swimmingly suspended in the fluid, whereby the liver is enclosed in the protective cover, so that the liver itself does not come into direct contact with dialysate storage fluid. In practice, slight differences may often occur between the densities between the organ and the dialysate. If the density of the dialysate is somewhat greater, the liver swims on the dialysate; if it is somewhat smaller, the liver slowly sinks. In these cases, the protective cover that is attached to the wall of the chamber takes up the partial weight forces from the liver, as necessary, to maintain the liver in its suspended state. This partial weight of the liver is relatively small and the protective cover is able to support this weight without causing pressure

points on the organ tissue. The connectors to the blood vessels in the organ are always flexible hoses and take up practically none of the forces exerted by the liver in the storage fluid. In effect, the liver floats or hovers in the storage fluid, primarily because of the density of the dialysate.

19. With regard to this rejection, Applicants submit that it is known to maintain a liver in a water-filled perfusion chamber and, further, that it is known that the density of the dialysate is much greater than that of water, because of the additives of sodium chloride, sodium bicarbonate, etc. to the dialysate solution. Thus, it would be readily apparent to the person of ordinary skill in the art that, once it is made known that the perfusion chamber is filled with dialysate, that a conventional dialysate would provide a greater buoyancy to the liver than does water. Applicants respectfully submit that the disclosure is adequate with regard to maintaining the organ in a suspended state in the storage fluid.

20. Further to 35 U.S.C. § 112, first paragraph, rejections on pages 3 – 4 of the Office Action, Examiner has rejected claims 5 – 11 as failing to teach or diagram how the PCS and DCS subcircuits are connected to each other to accomplish the task of the dialyzing the perfusate. Dialysis of perfusate to maintain the vitality of an extracorporeal organ is well known in the field of organ transplantation and it is not necessary to teach the details of the integration of the two subcircuits. Indeed, various embodiments of the two subcircuits are included within the scope of the present invention. In other words, the dialysis step and the dialysis equipment per se are not inventive features of the claimed storage system. What is an inventive feature is that the perfusion chamber itself serves as a reservoir or storage container for the dialysate, which flows into the DCS subcircuit as needed. Applicants respectfully submit that the written description

requirement is met, that the specification contains sufficient description of the equipment so as to reasonably convey to one skilled in the art of organ transplant surgery, that the inventors had possession of the claimed invention at the time the application was filed. Applicants therefore request that Examiner withdraw the rejection.

21. Further to 35 U.S.C. § 112, second paragraph, rejections on pates 4 – 5: Examiner rejected claims 5 – 11 because it is unclear to Examiner how the dialysate and the perfusate are two different solutions. The person of ordinary skill in the art is one who is familiar with extracorporeal organ preparation for transplant surgery. That person most certainly understands that "perfusate" is the solution that is used to perfuse an organ and that "dialysate" is a solution that is used to cleanse the perfusate of metabolic waste products. To "perfuse" an organ is to provide a flow of a solution through the organ in order to maintain its vitality. The perfusate is typically blood or blood with electrolytes or other substances added to it, or, as disclosed in Brasile, a non-blood physiologic solution that is capable of maintaining cellular integrity. See Brasile, col. 3, paragraph [0033]. Applicants note that the 2001 article by Michael R. Schön et al. mentioned above describes a well-known method of Normothermic Extracorporeal Liver Perfusion (NELP), which shows in detail the perfusion circuit and the dialysis circuit and gives details on the perfusate and dialysis solutions. The actual composition of the perfusate will vary depending on the organ and type of animal. In the case discussed in the article, the perfusate was pig blood and a balanced electrolyte solution and the dialysate was not further described, other than to say, 10 Liters of dialysate, which indicates that the dialysate is a commercially available common dialysate. See *Schön article, 3rd page, first column.*

22. Applicants submit that the terms "perfusate" and "dialysate" are very well known in the science and practice of organ transplant and that lack of a description of these types of solutions does not result in indefiniteness. Applicants further submit that the art and techniques of dialyzing perfusate are well known and that the functioning of the storage system with its claimed inventive features does not rely on a particular dialysis technique, only that the dialysate stored in the perfusion chamber flow into the dialysis circulation system. Accordingly, Applicants submit that the claims do, in fact, particularly point out and distinctly claim the subject matter which Applicants regard as the invention, that is, a perfusion chamber filled with dialysate as a storage fluid.

23. **Examiner's Re-Write of Claim 5:** Examiner has re-written claim 5 so as to diminish the distinction between the perfusate circulation system and the dialysate circulation system. Applicants note that the perfusate and the dialysate are both vitality-preserving fluids. In other words, the term "vitality-preserving fluid" is an overarching term that encompasses both "perfusate" and "dialysate." See Paragraph [0008] of the Specification as originally filed. For purposes of clarity, the term "vitality-preserving fluid" should not be used to refer exclusively to perfusate or dialysate. The fluid that flows through the organ is the perfusate and not the dialysate. For this reason, Applicant objects to Examiner's re-writing of claim 5 to read as follows: "... said vitality preserving fluid circuit comprises a dialysate circulation system (DCS) and a perfusate circulation system (PCS) that administers and recycles the vitality preserving liquid as it flows through the organ; ..." Underlining was added to point out the specific text to which Applicants object.

24. Applicants further object to Examiner's re-write of the remaining sub-paragraphs of claim 5 as being unclear and request that Examiner examine claim 5 as provided by

Applicants. Claim 5 has been amended to clarify the language with regard to the vitality-preserving fluid circuit and its subcircuits. The remaining sub-paragraphs of the claim 5 are written in clear and precise terms.

25. **Rejections under 35 U.S.C. § 102(b):** Examiner has rejected claims 5, 6, and 11 as being anticipated by Brasile (U.S. Patent Application Publication # 2002/0012988), finding that previously presented arguments were not persuasive. Claim 5 recites a limitation that the protective cover encloses the organ within a space defined by the protective cover and a portion of the wall of the chamber, and that the cover provides a complete barrier between the organ and the storage fluid. Currently amended claim 5 further recites that the organ is maintained in a suspended state and completely surrounded by the storage fluid, which is a dialysate. Brasile discloses a method of supporting an organ on a pad or in a sling 36. The organ is not maintained surrounded by a storage fluid. There is no fluid storage in the Brasile perfusion chamber (32), but rather, liquid is drained from the organ via tubing 43 and drips down into a perfusate collection reservoir 38 beneath the organ support.

26. Applicants respectfully submit that Brasile does not teach or suggest the inventive features recited in claim 5 as currently presented and requests that Examiner withdraw this rejection of claims 5 and all its dependent claims 6 – 11.

27. **Rejections under 35 U.S.C. § 103(a):** Examiner repeated the rejections of claims 5 – 9 and 11 as being obvious over Brasile and claims 5 – 11 over Brasile in view of Bacchi et al. (U.S. Patent 5,285,657; 1994) as stated in previous Office Actions. Brasile teaches storing an organ supported on an organ support member in a perfusion chamber and Bacchi et al. teaches a thermally insulated enclosure. According to

Examiner, it would have been obvious to modify the invention of Brasile with the hermetically sealed lid taught by Bacchi et al.

28. The arguments presented above in response to the 35 U.S.C. § 102(b) rejections show that Brasile does not disclose or teach filling the organ perfusion chamber with dialysate, nor storing the organ enclosed in a protective cover and, except for the portion of the wall area that has the connectors, completely surrounded by the storage fluid in the perfusion chamber. Bacchi et al. also does not teach or disclose storing the organ in surrounded by a storage fluid in the perfusion chamber, the storage fluid being a dialysate. The combined disclosures of Brasile and Bacchi et al. do not disclose, teach, motivate one to implement, or suggest these two features. Thus, Applicants submit that the combined references of Brasile and Bacchi et al. do not render any of the claims of the present application obvious.

29. With regard to the rejection of claims 7 – 9: It is known to circulate a heated fluid through the perfusion chamber (Schön dissertation). The inventive step in these claims is integrating the heat source directly into the walls of the perfusion chamber.

30. All other claims deemed rejected by the combination of Brasile and Bacchi et al. are dependent claims that depend from claim 5 and, thus, contain all the limitations of claim 5.

31. Applicant submits that claims 5 – 11 contain allowable subject matter and requests that Examiner withdraw all rejections and allow all claims currently presented.

32. Examiner is kindly invited to call or email the Undersigned, should there be any issues that can be quickly clarified with this type of communication.

33. This paper is being filed within three months of the issue date of the Office Action. An IDS with the additional references is being filed concurrently with this paper and arrangements for payment of the necessary fees are provided.

Respectfully submitted,

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Claims of co-pending application
Attachments A – D
Translator's Statement